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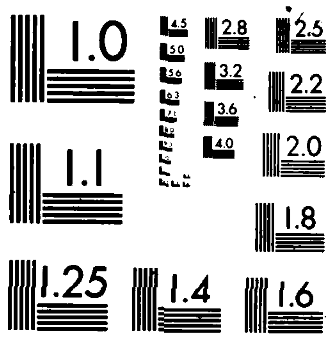

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EFFECTS OF IONIZING RADIATION AND RESTRAINT STRESS ON ACTIVITY, AVOIDANCE CONDITIONING, AND STOMACH ULCERS IN ALBINO RATS

Jackie Lanum, Ph.D.
Dennis W. Blick, Ph.D.
Michael E. Campbell, Ph.D.
Thomas G. Wheeler, Ph.D.
Stephen A. Koger, B.A.
Michael R. Murphy, Ph.D.

Systems Research Laboratories, Inc.
2800 Indian Ripple Road
Dayton, Ohio 45440-3696

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Brooks Air Force Base, Texas 78235

NOTICES

This final report was submitted by Systems Research Laboratories, Inc., 2800 Indian Ripple Road, Dayton, Ohio 45440-3696, under contract F33615-80-C-0603, job order 7757-05-43, with the USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas. Captain Thomas E. Dayton (USAFSAM/RZV) was the Laboratory Project Scientist-in-Charge.

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

Thomas E. Dayton

THOMAS E. DAYTON, Captain, USAF
Project Scientist

Donald N Farrer

DONALD N. FARRER, Ph.D.
Supervisor

Royce Moser Jr

ROYCE MOSER, Jr.
Colonel, USAF, MC
Commander

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In an experiment with albino rats, we have tried to model a nuclear attack scenario in which military personnel receiving 600 to 800 rads of ionizing radiation would be making a counterattack under the stress of an emergency situation. We used a dose of radiation that, though higher than the human exposure field, was estimated to be its physiological equivalent. Restraining the rat in an immobile position, a technique previously shown to have stressing qualities for rats, was chosen as an analogy to the stress of being in a war emergency. Activity and conditioned avoidance acquisition were chosen as test responses.

Performance in the activity maze was affected only to a minor degree and in the direction of considering irradiation as activating. However, all irradiated groups showed retarded conditioned avoidance acquisition, which can be interpreted as decreased adaptability to a stressful situation. Further, our results support the expectation of performance decrements in the military scenario that could not be predicted by considering ionizing radiation in isolation. On the avoidance task, male rats in the combination stress-irradiation

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condition showed more failures to respond and longer response latencies than any other group. Female rats, on the other hand, showed shorter escape/avoidance latencies in the combined stress-irradiation condition than in the irradiation condition alone. This sex difference may be useful as a clue for investigating mechanisms of radiation resistance and interactions between stressors.

EFFECTS OF IONIZING RADIATION AND RESTRAINT STRESS ON ACTIVITY, AVOIDANCE CONDITIONING, AND STOMACH ULCERS IN ALBINO RATS

INTRODUCTION

Following a nuclear attack, US Air Force personnel not directly injured by the blast and thermal effects would be expected to make immediate military responses and to perform their preassigned missions after exposure to as much as 700 to 800 rads, an amount in excess of the lethal dose ($LD_{50/30}$) (6). Such an exposure would produce the prodromal clinical syndrome of vomiting, fatigue, anorexia, and malaise that has been described by Gerstner (20). Zellmer (54) speculated that efficiency would be reduced by about 20% by the end of the first day following exposure to 600 rads of ionizing radiation. A review of the experimental literature suggests that the performance effects will depend on the nature of the task required.

The effects of ionizing radiation have been studied extensively on complex behaviors that depend on learning and retention. Radiation malaise is reflected experimentally by decreases in spontaneous activity and increases in reaction time or response latency (8, 17, 22, 23, 26, 28, 29, 30, 44, 52). Except for the slowing of reaction time, very few immediate negative behavioral effects occur unless radiation exposure is much greater than 700 rads (see 9, 15, 16, 24, and 39 for reviews). Taste aversions are readily produced to a gustatory stimulus associated with ionizing radiation (19), but when care is taken to avoid motivational decreases due to the change in reinforcement value of food, no decrements in performance on instrumentally conditioned tasks are apparent in nonprimates. Primates have been tested on more complex problem-solving tasks with similar results. In studies at the USAF School of Aerospace Medicine (USAFSAM), Brooks Air Force Base, Texas, Yochmowitz and Brown (52) and Yochmowitz et al. (53) tested the effects of different rates of ^{60}Co exposure to a total dose of 300 rads and found only slight deficits in primate performance despite the presence of the prodromal syndrome.

This study differs from previous studies by attempting to take into account other stressors that would occur concomitant with the radiation exposure. We felt that a realistic appraisal of the situation should consider the psychological and physiological impact of the emergency situation. The stress of having been subject to nuclear attack, as well as the physical and mental stress involved in mounting a counterattack, could interact with the radiation effects. We adopted an animal model of generalized stress previously developed in our laboratory and added radiation as a variable to examine particular interactions. Although rodents are less like humans, both cognitively and behaviorally, than are primates, we felt that a rodent model could test the validity of our assumptions and determine the relevant parameters for the more efficient use of primates should subsequent studies be necessary.

We previously have shown that a generalized stressor for rats (immobilization restraint) decreases activity and inhibits ability to learn a two-way shuttle avoidance response (25). Overall, the amount of stress was positively correlated with performance decrements and the incidence of stomach ulcers. The use of negative reinforcement in avoidance conditioning is analogous, in a general way, to the aversive conditions of war. In an operational sense, radiation is a noxious stimulus because animals will avoid irradiated areas or stimuli that are associated with irradiation (18, 19). Several previous studies have led us to expect that behavior sensitive to stress also might be sensitive to radiation (33, 37, 51).

Both male and female rats were included in this study to see if interactions between stress, radiation, and sex would be found that could have implications for our understanding of the basic mechanisms and eventual control of such effects. We previously found maximum performance decrements in males at lower levels of stress than in females (25). Following 10,000 rads of ionizing radiation, Mickley (33) found immediate decrements in avoidance performance that were less severe in female than male rats. He hypothesized that females exhibit greater immune responsiveness that makes them both more stress and radiation resistant.

METHODS

Choosing a Level of Ionizing Radiation

Since rodents are less sensitive to ionizing radiation than humans are, we chose an experimental dose level based on an analysis of comparable effects. A standard method of measuring a physiological effect of radiation is by calculating the number of subjects that die from an exposure in a given time period. Available data suggest that the midline dose in a rat must be 2.5 to 3.5 times higher than that in man to produce equal lethality in terms of $LD_{50/30}$ (6). Based on this and the differences in the incident and midline tissue dosage of radiation in the two species (40), we estimated that 600 to 800 rads of ionizing radiation for man is equivalent of 1400 to 2000 rads of ionizing radiation (^{60}Co 1.2 MeV source) for rats. We chose 2000 rads (midline) as the level of exposure for the initial experiment to maximize the possibility of an effect. If an effect occurred at this highest reasonable dosage, dose response relationships and thresholds could be investigated in later experiments.

Choice of a Stressor

Previous experiments were conducted to find a stressor that was not a direct physical insult to the animal but nonetheless produced effects on activity, avoidance conditioning, and ulcer incidence. The rats were restrained by wrapping them securely in an envelope of screen wire, and this technique was found to be both simple and effective. Restraint time was, in general, correlated with the magnitude of effects. The relationships between restraint duration and mean number of avoidance responses (per 60 trials) and stomach lesions are presented graphically in Figures 1 and 2 respectively (25).

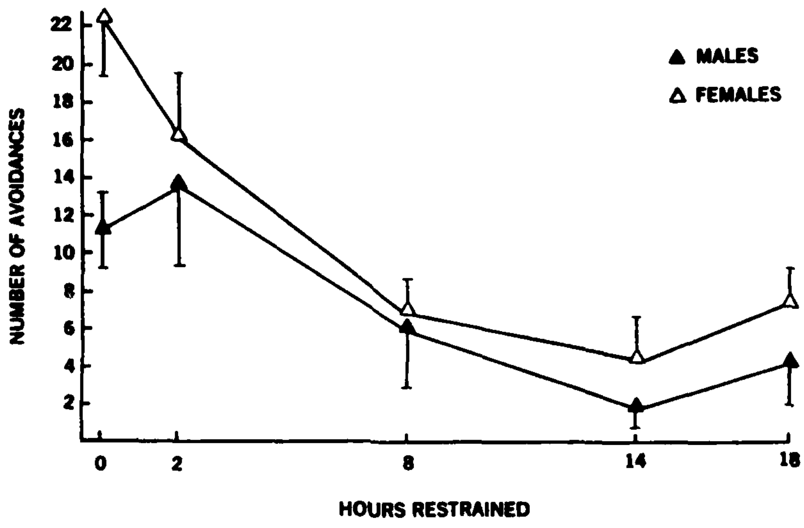

Figure 1. The mean number of avoidances (± 1 S.E.M.) shown by male and female rats after 0, 2, 8, 14, and 18 hours of restraint stress.

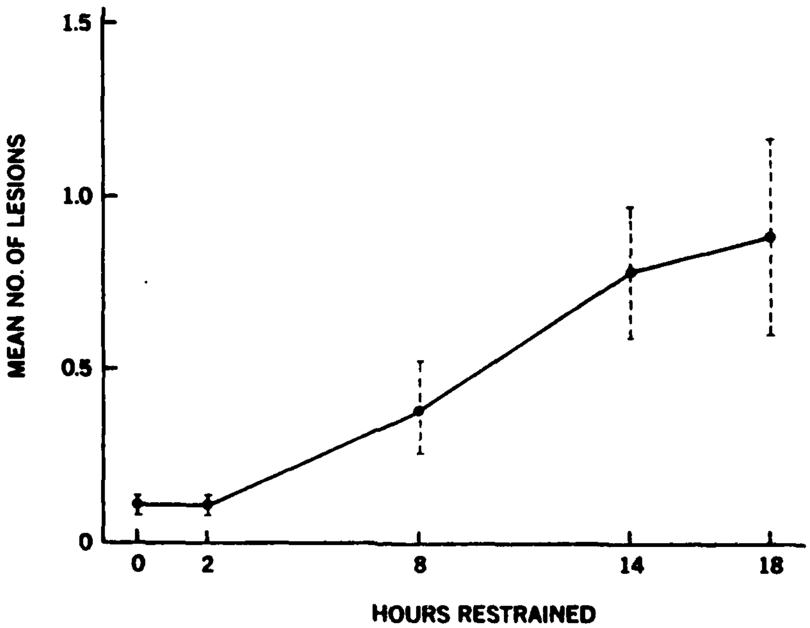

Figure 2. The mean number of stomach lesions (± 1 S.E.M.) after 0, 2, 8, 14, and 18 hours of restraint stress.

For the current experiment, eight hours of restraint was chosen because of the previously demonstrated intermediate level of effect. A combination of radiation with this level of stress could result in either increments or decrements in performance.

Subjects

The subjects were 36 male and 36 female Sprague-Dawley rats, obtained at 72 days of age from Harlan Industries, Indianapolis, Indiana. They were given ad libitum access to food and water, and were maintained on a 12-hour-on and 12-hour-off light-dark cycle for 4 weeks prior to experimentation.

Equipment

Activity levels were recorded in two standard open-field mazes, 3 ft (91.4 cm) square with 1-ft (30.5 cm) wall height. Nine 1-ft (30.5 cm) squares were marked on the maze floor. The mazes were constructed of plywood, painted with glossy white enamel for ease in cleaning between trials. The mazes were located in the center of a large room, approximately 2.6 m beneath a bank of 40 W fluorescent lamps. Observers were seated on stools at opposite corners of each maze. No visible shadows were cast on the maze floor by either the observers or the maze walls.

Avoidance testing was performed in three shuttle-boxes modeled after Lafayette Instrument Company's "Modular Testing Unit 8500." The two compartments of each shuttle-box had floors of stainless steel bars that could be independently electrified. The compartments were connected by an opening, and the weight of a rat on the grid floor closed a switch to indicate the rat's location. Shock was delivered to each grid by a Coulbourn Model E13-16 Shock Distributor. Small, dim incandescent lamps were located in the ceiling of each compartment above Plexiglas diffusers. The top half of the front wall of each chamber was made of half-silvered ("one-way") glass to allow the experimenters to observe the subject. The shuttle-boxes were interfaced with a laboratory computer (NOVA 800) that was used to control the schedule and duration of stimuli delivered to the rat and record the rat's response. (For details concerning the data acquisition system see Blick et al. (5) and Lanum et al. (25)).

All irradiations were performed using the USAFSAM Atomic Energy of Canada Ltd. (AECL) Eldorado 78 teletherapy unit, a cobalt-60 gamma irradiation unit with a nominal source strength during the course of the study of approximately 6400 curies. The midline dose rate was determined using ionization measurements made in cylindrical (5 cm diameter) water-filled phantoms approximately the size of the animals used in the study. The phantoms were exposed in the same boxes used to expose the animals. The ionization instrument was a Victoreen Model 100 IC probe first calibrated against National Bureau of Standards (NBS) calibrated ionization chambers on the AECL cobalt-60 source. Exposure readings were taken at phantom midline and converted to tissue rads by application of a roentgen to rad conversion factor of X 0.94. All exposure readings were standardized to 195.2^{0}K and

760 mm Hg. The animal entrance and exit doses were measured using cobalt-60 calibrated thermoluminescent dosimeters (TLDs) (Harshaw type 100 LIF power) exposed on the cylindrical phantoms inside the exposure boxes. A midline dose calculation with TLDs gave agreement with the ionization values to within ± 2%.

To cage the rat during irradiation, individual Plexiglas boxes (7.5 cm X 25 cm X 20 cm) were constructed with holes at either end for breathing and the rat's tail. The sides were open so that a 5-cm-thick Styrofoam block could be placed on each side of the rat and held in place by Velcro bands. This configuration allowed easy adjustment to rats of different sizes. Three individual Plexiglas boxes were slipped into a Plexiglas transport cage (17 cm X 20 cm X 27 cm) for ease of carrying to the irradiation source. The radiation field size at the exposure midplane was approximately 35 cm X 35 cm to obtain the appropriate dose rate. Therefore, a carrier of three rats could be placed in front of the source and uniformly irradiated. Figure 3 is a diagram of the source and the arrangement of the rats for irradiation.

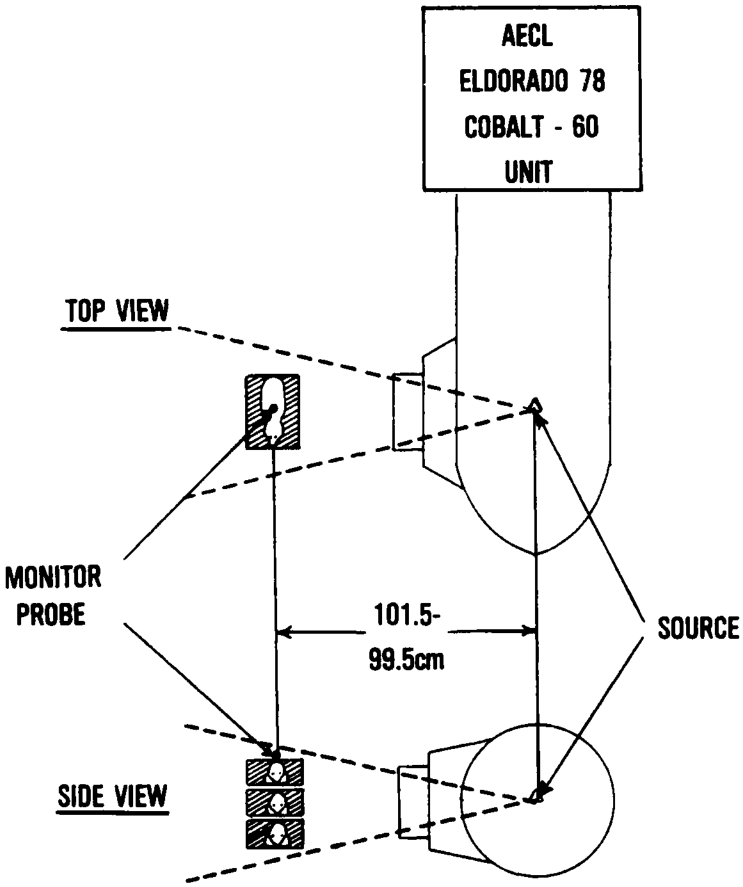

Figure 3. A diagram of the ^{60}Co radiation source and the location of the rats during irradiation.

Procedure

Each animal was handled and weighed each day for 5 days. At approximately 100 days of age, 9 male and 9 female subjects were randomly assigned to each of the experimental conditions: (a) sham irradiation, (b) restraint stress plus sham irradiation, (c) irradiation, (d) restraint stress plus irradiation.

The animals were housed and behaviorally tested on the 4th floor of one building and irradiated in the basement of another building. All animals were given a three-day adaptation period to minimize the potential stress of the sham and irradiation procedures. A pilot study determined three days to be the minimum time necessary to obtain activity and avoidance behavior comparable to a control group not subjected to these disturbances. During the adaptation period, each rat was snugly secured (unable to turn around) in an individual Plexiglas box; and placed in a transport cage with two other rats. Then the animals were taken to the test site where they were placed on the table in front of the inactive teletherapy unit for 20 min before being returned to the animal quarters and placed in individual cages. All animals were carried at the same time of day (0800-1200) and in the order used on the test day.

On the fourth day, all animals were deprived of food for 24 hr and water for 8 hr prior to testing. Animals in the sham and irradiated groups remained in their home cages during this deprivation period. Each animal in the restraint and the restraint plus irradiation groups was held immobile for 8 hr prior to testing. Immobilization was accomplished by placing the rat near the edge of a piece of aluminum hardware cloth, and then rolling the cloth into a tube that surrounded the rat. The ends of the screen wire tube were twisted and secured with galvanized wire. Care was taken to wrap the screen wire tight so that the subject could not turn around, but not so tightly as to compress or twist the animal into an abnormal position. Each wrapped animal was placed into a plastic tray in an upright position. Experimental subjects were always restrained in a separate room and never returned to the colony because of the potential for stress communication through pheromones. For the same reason, immobilized animals were always carried separately and tested after animals from other groups tested the same day. After each day's testing, the apparatus was washed with alcohol and allowed to dry overnight, to minimize odor transfer between groups.

Animals in the sham control group were removed from their home cages and transported to the ^{60}Co source and remained for 20 min in the source room. The restraint plus sham group was unwrapped from the hardware cloth, immediately placed in the Plexiglas carriers, and treated similarly to the sham control group.

All procedures were the same for the irradiated and the restrained plus irradiated animals, but the radiation source was activated. The Plexiglas boxes were placed 100 cm from the source with Styrofoam block sides facing the gamma beam (see Fig. 3). These animals were given 2000 rads of gamma irradiation delivered at 100 rad/min for 20 min.

After time in the irradiation room, each animal was returned to the laboratory for behavioral testing. Prior to activity testing, each animal was placed in a transport cage for 10 min with access to water. All aspects of the procedure were timed carefully so that testing began 20 min after irradiation. Then the animal was placed in the center square of the open-field maze, and the following data were recorded independently by two observers for 5 min: (a) latency to leave the center square; (b) total number of lines crossed (ambulations); (c) number of center square crossings; (d) number of grooming episodes; (e) number of rearing episodes; and (f) number of fecal boli excreted.

After activity measurement, each animal was taken (via a transport cage) to an adjacent room for escape/avoidance testing. Escape/avoidance testing occurred in a darkened room, and began with the animal in the shuttle chamber for a 5-min adaptation period prior to testing.

The small end-wall lamps were "ON" during the adaptation period, allowing the experimenter to observe the rat. The overhead lamps on each side of the chamber were programmed to be the primary conditioned stimulus (CS), since they were more salient than the end-wall lamps. The program consisted of a 5-sec CS period, during which both the overhead and end-wall lamps flashed at a 2-Hz rate on the side of the chamber where the rat was located. If the rat did not move to the other compartment of the shuttle-box, an unconditioned stimulus (US) consisting of a (30-ms duration) pulsed 0.2 mA shock was administered at a 2-Hz rate (synchronous with the light flashes) until the animal moved to the other compartment, or until 15 sec had elapsed. The CS (and the US, if present) terminated when the animal moved to the other compartment. If a rat stood in the doorway with its feet on both grids, shock was briefly delivered to both grids in sequence, and the CS was delayed 10 sec. CS-CS intervals were randomly selected from a range of 25 to 55 sec, with a mean of 40 sec. Each animal received 60 trials. Latency to respond from CS onset was recorded for each trial. The trials in each session were categorized and counted as either: (a) failure to respond (no response for the 20-sec CS-US duration); or (b) an escape (response during the US); or (c) an avoidance (response during the CS). The number of trials to achieve a learning criterion of 8 avoidances in 10 trials was recorded.

Within 1 hour following avoidance testing, each animal was euthanized (Halothane overdose). The stomach was removed, opened, and examined for ulcers, which were specified by the number and approximate length of the lesions. The adrenals were removed and placed in individually identified vials of cold saline. Residual fat was carefully removed from the glands, which were weighed within 2 to 4 hours following removal.

The USAFSAM Comparative Pathology Branch (VSP) completely necropsied several animals from each group to assure the general health of the animals.

RESULTS

Activity Maze

A 2 X 2 X 2 (sex X restraint X irradiation) analysis of variance was performed for each of the measurements recorded in the activity maze (latency to leave center square, ambulations, groomings, rearings, center square crossings, and fecal boli). Significant effects were found in latencies to leave the center square and in number of grooming episodes.

The latency to leave the center square showed a main effect of sex ($p<.01$), a two-way interaction of restraint and irradiation ($p<.01$), and a three-way interaction of sex, restraint, and irradiation ($p<.05$). Group means and standard errors are shown in Figure 4. The interactions are presented in Figure 5. With the exception of the irradiated groups, the males had a generally slower response with the maximum difference occurring in the sham control males which took the longest time to leave the center square. Irradiation markedly decreased the response time for subjects that were not restrained but did not change or slightly increased the response time for restrained subjects.

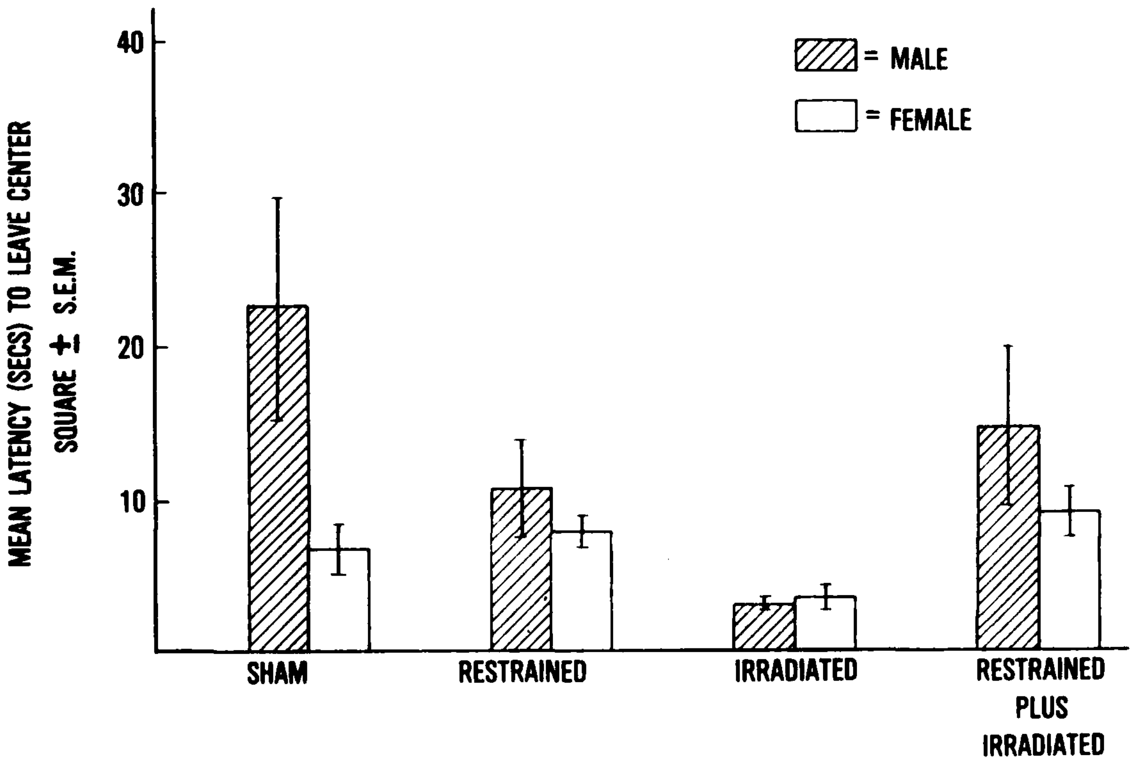

Figure 4. The mean latency in seconds (± 1 S.E.M.) to leave the center square of the activity maze for male and female rats in the sham control, restraint stressed, irradiated, and both restrained and irradiated groups.

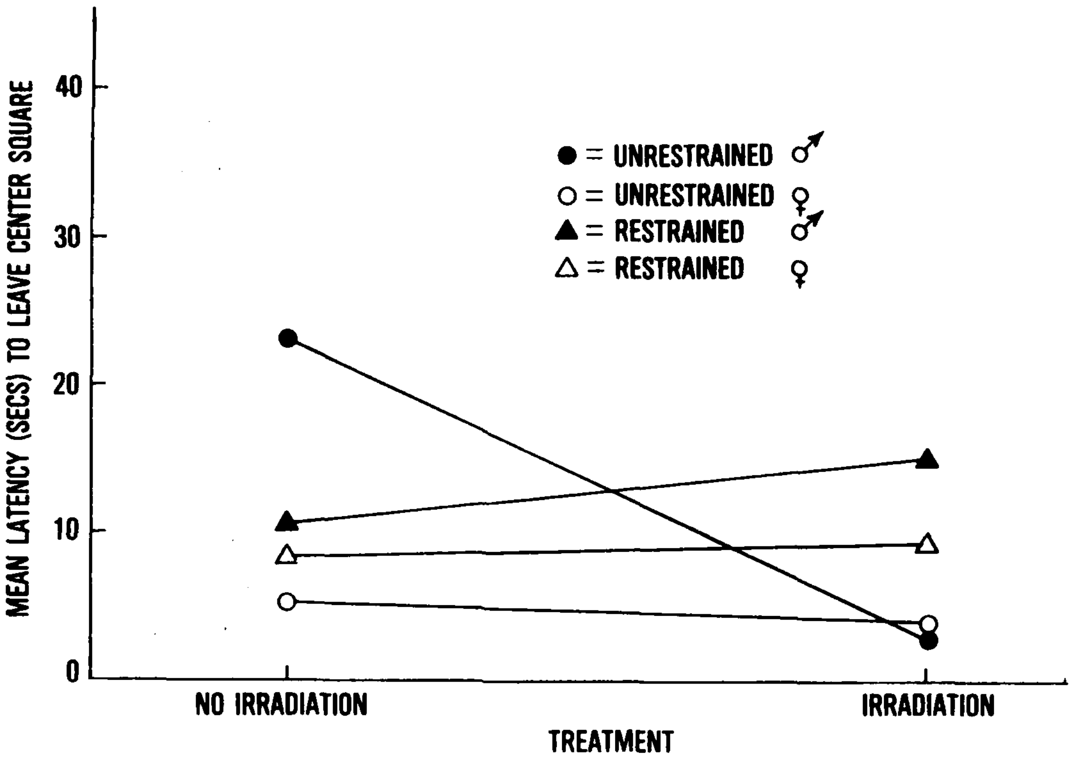

Figure 5. A comparison of the mean latency in seconds to leave the center square of *the activity maze for male and female* rats as a function of restraint and irradiation condition.

The number of grooming episodes showed a significant effect of radiation treatment ($p<.05$), a two-way interaction of restraint and irradiation ($p<.05$), and a three-way interaction of sex, restraint, and irradiation ($p<.01$). Figure 6 shows that there was some increased grooming in all treatment conditions, the increase among irradiated males was the most dramatic. Restraint caused a slight increase in grooming, except in irradiated males where a reduction in grooming was seen (Fig. 7).

In summary, performance in the activity maze was generally unchanged by the experimental treatments on all but two parameters. Latency to leave the center square was decreased, particularly in the irradiation condition. Because we tested fairly soon after irradiation (20 min), we may have been within the range of increased sensory activation reported for low-level ionizing radiation (7, 24, 48). Decreased alertness or radiation malaise would have been expected if we had tested at later times during the day or at higher levels of irradiation (14, 48). The increased grooming seen in the irradiated condition corresponds well with increased self-care or self-directed activity previously seen in primates (28, 29, 30).

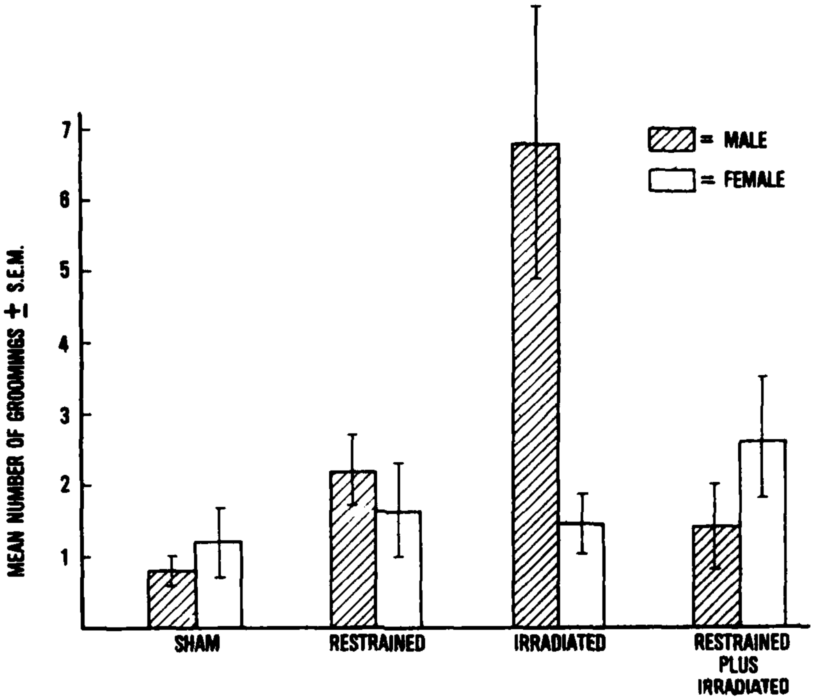

Figure 6. The mean number of grooming episodes (± 1 S.E.M.) during 5 minutes in the activity maze for male and female rats in the sham control, restraint stressed, *irradiated, and both* restrained and irradiated groups.

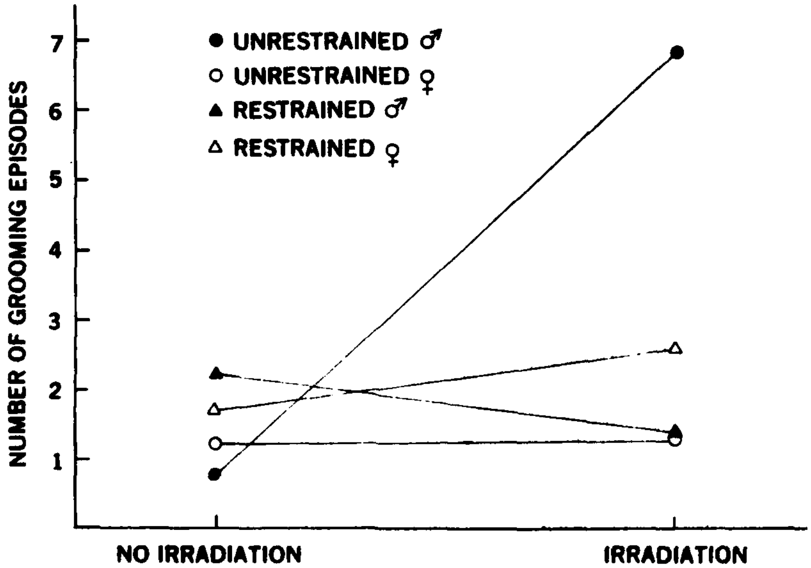

Figure 7. A comparison of the mean number of grooming episodes during five minutes in the activity maze for male and female rats as a function of irradiation and restraint condition.

Avoidance

The computer automatically recorded shuttle-box latencies--the time between the light onset (CS) and the response, which involved moving to the opposite compartment of the shuttle-box, where the rat's weight on the grid closed a microswitch. This latency should be distinguished from the latency to leave the center square of the activity maze, seen in the previous section. The response latencies from 60 trials were averaged across blocks of 10 trials for each subject and then analyzed by repeated measures analysis of variance (sex X restraint X radiation X blocks). Sex ($p<.001$) and radiation ($p<.001$) showed significant main effects and interactions ($p<.05$). Duncan's multiple range test was applied to further analyze the interactions (13).

The results are shown in Figures 8, 9, and 10. Figure 8 shows that group latencies vary by treatment, with both sham and restrained groups showing more rapid responses than either irradiated or restrained plus irradiated. Further breakdown by sex (Figs. 9 and 10) shows that the results are not unitary. Females generally responded more rapidly ($p<.001$) and the irradiated subjects, with the exception of the restrained females, responded more slowly ($p<.001$ with a $p<.05$ interaction).

The significant latency X blocks interaction ($p<.001$) was typical of learning curves. The radiation X blocks and blocks X sex X radiation interactions were also significant ($p<.001$). To visualize these results in detail, Figure 11, views A through D, compare the latency to respond for males and females on each block of trials in each treatment condition.

Sham controls showed decreasing latencies across trials to a plateau in a fashion generally typical of learning curves (Fig. 11, view A). As in our previous experiment (25), only females avoided frequently enough to have a group mean less than 5 sec (avoidance). Restrained animals also showed fairly typical learning curves, but females responded at the same level as the males (Fig. 11, view B). In the irradiated groups, there were no decreases in latency for males; although a slow decline in latencies occurred for females, no plateau was reached during 60 trials (Fig. 11, view C). The most dramatic sex differences occurred in the combination restrained and irradiated groups (Fig. 11, view D). The males began with longer latencies and did not show any consistent declines across blocks; the females began with shorter latencies which declined in a negatively accelerated manner to a plateau. These curves suggest that restrained and sham control animals showed relatively normal learning, while irradiated and restrained plus irradiated males failed to show avoidance learning. Irradiated females showed a reduced but moderate degree of learning, but females that were restrained plus irradiated showed learning that was indistinguishable from those merely restrained.

A Duncan's multiple range test confirmed these impressions. The female treatment groups fell into three categories significantly different from each other at $p<.05$ (Fig. 12). Mean response latencies for sham were controls shorter than those of any other group. Latencies of restrained and restrained plus irradiated groups were not significantly different from each

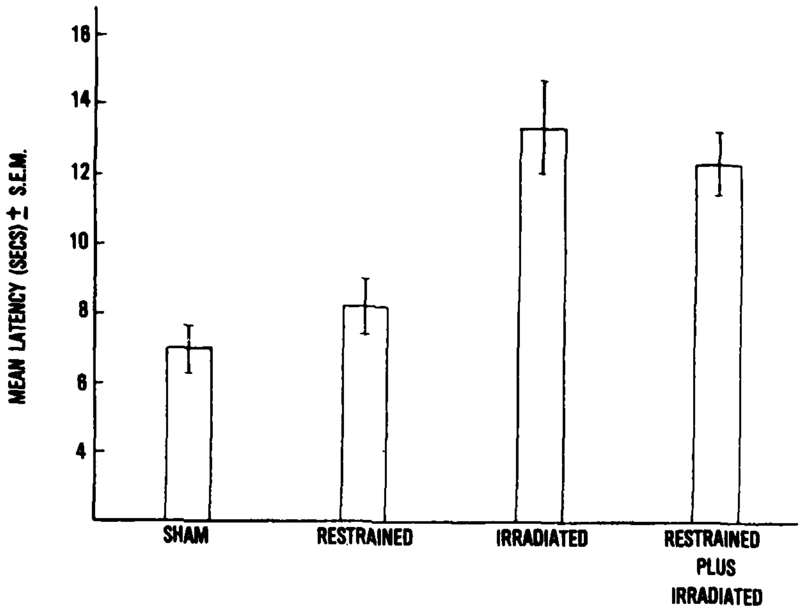

Figure 8. The mean avoidance latency (± 1 S.E.M.) following CS onset for sham control, restraint stressed, irradiated, and restrained plus irradiated groups. Data is averaged from an equal number of male and female subjects in each group.

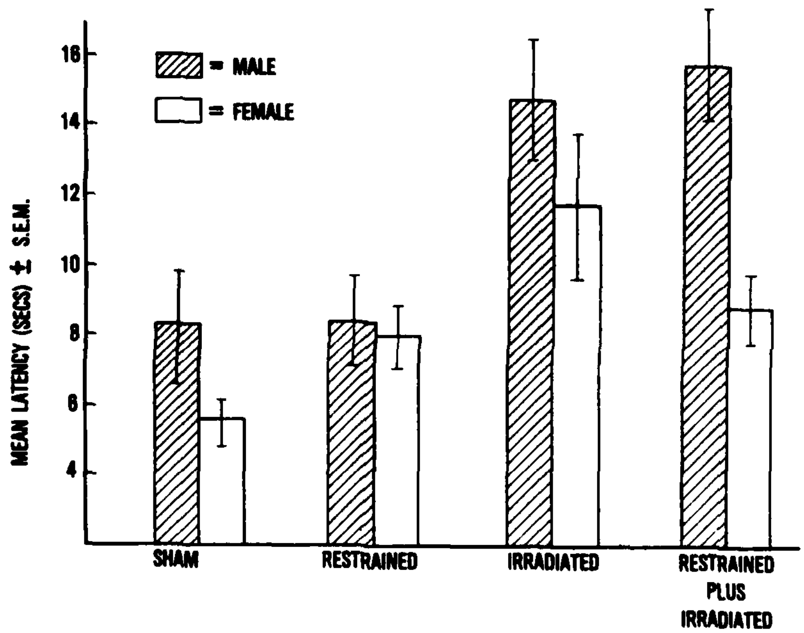

Figure 9. The mean avoidance latency (± 1 S.E.M.) following CS onset for male and female rats in sham control, restraint stressed, irradiated, or restrained plus irradiated groups.

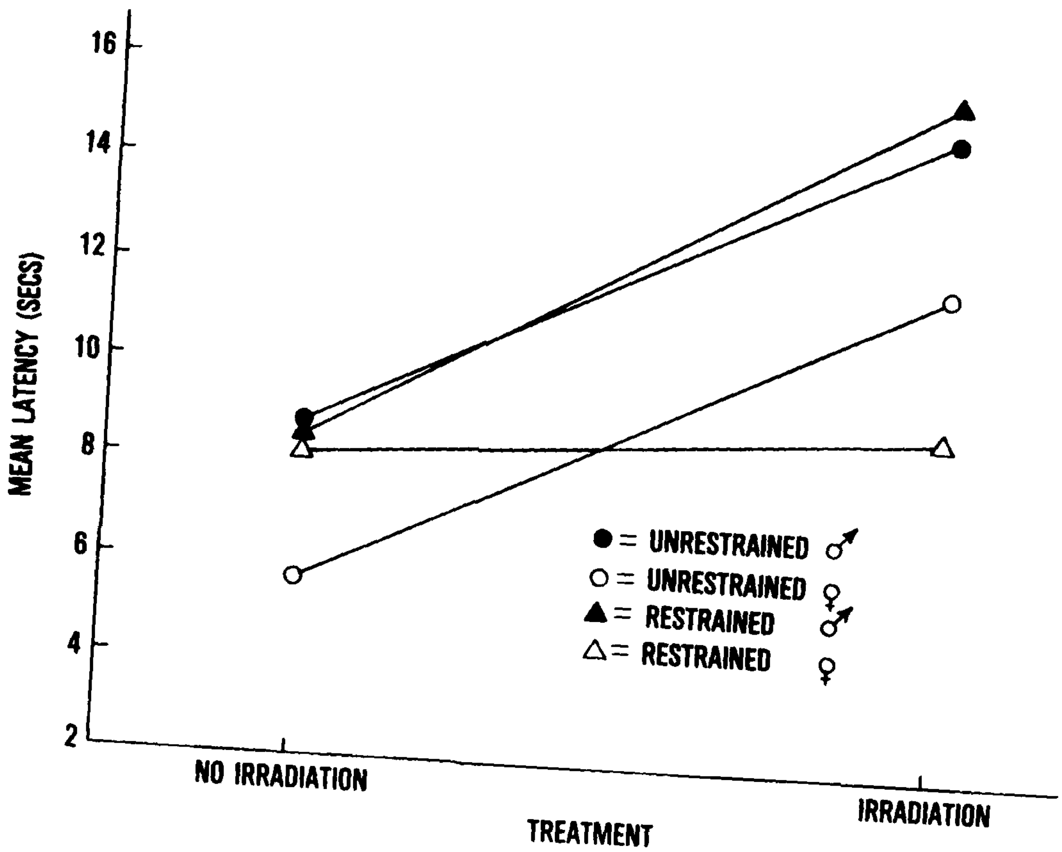

Figure 10. A comparison of the mean avoidance latency (± 1 S.E.M.) following CS onset for male and female rats as a function of restraint and irradiation condition.

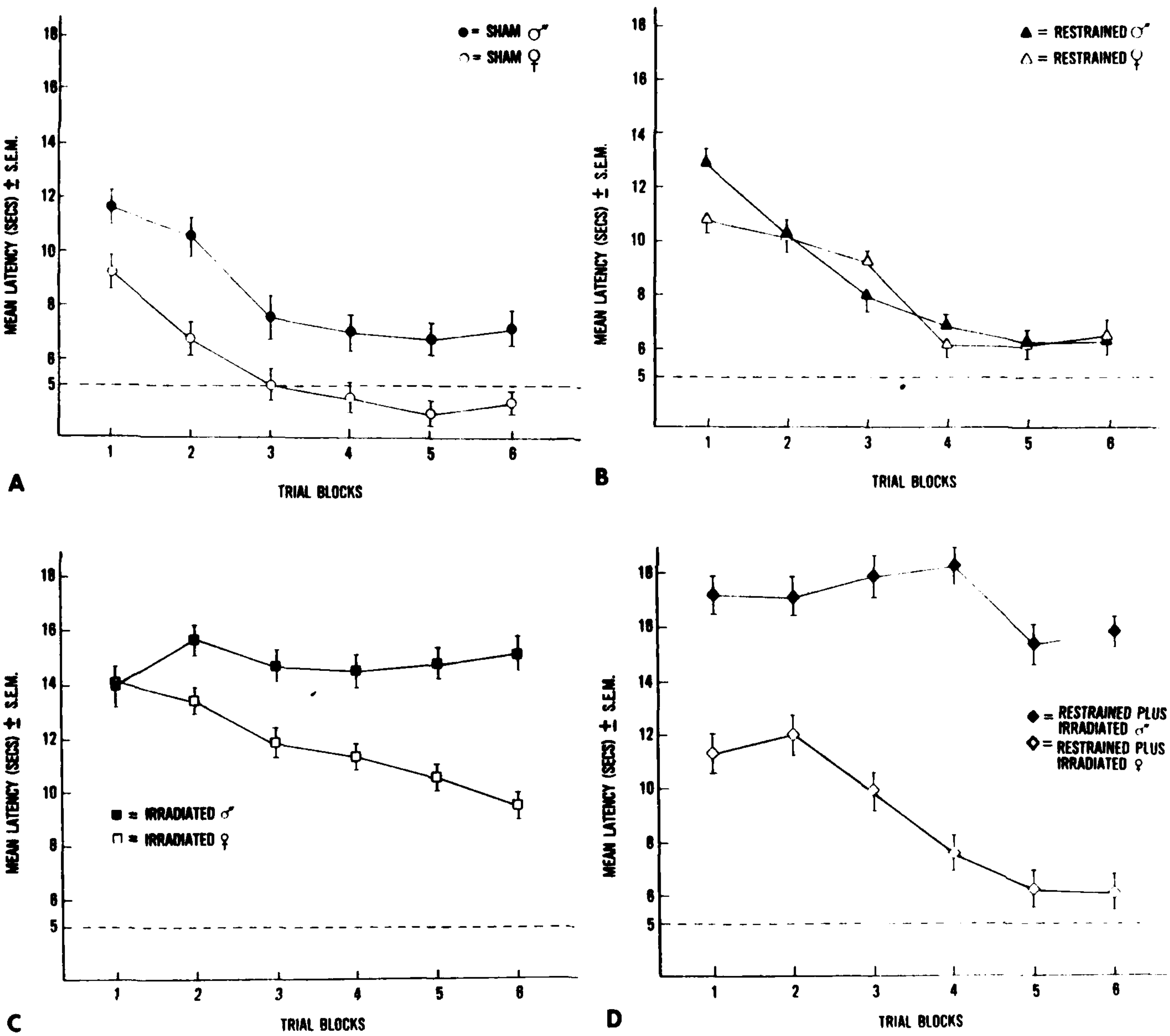

Figure 11. Learning curves for male and female rats in each of the experimental conditions. The mean avoidance latency ($\pm$ 1 S.E.M.) is plotted for each block of ten trials (total = 60 trials) in sham control (A), restraint stressed (B), irradiated (C), and combination restraint stressed and irradiated conditions (D).

RESPONSE LATENCY

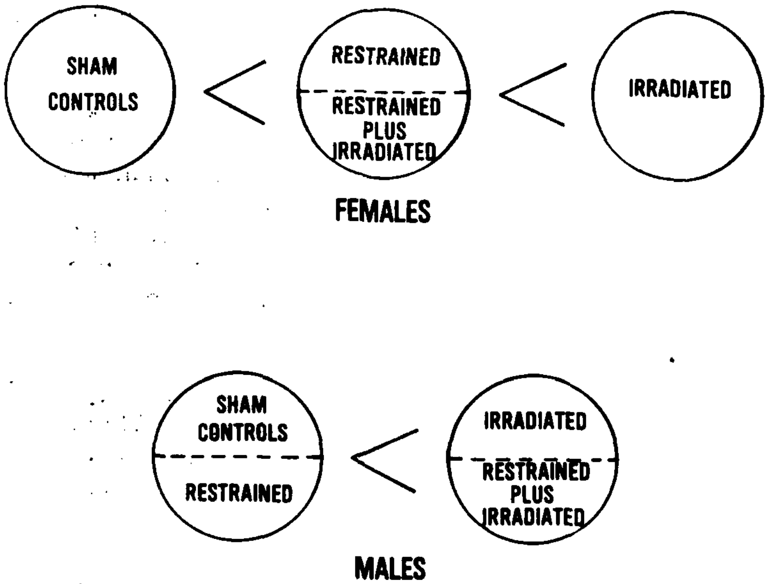

Figure 12. A diagramic representation of the similarities and differences in mean avoidance latency between treatment groups of females and males. The response times increase from left to right with a significance level of $p < .05$ or greater (Duncan's procedure) between groups.

other but were shorter than those of irradiated females. Conversely, mean response latencies for males fell into only two categories ($p<.05$): (a) sham controls were not significantly different from restrained subjects; (b) irradiated males were not significantly different from restrained plus irradiated males. However, the former (sham and restrained) had significantly shorter latencies than the latter (irradiated and restrained plus irradiated).

An additional way of analyzing these response latencies is to separate them into mutually exclusive response categories. Each response can be categorized as either: (a) a failure to respond (latency greater than 20 sec); (b) an escape (latency greater than 5 sec but less than 20 sec); or (c) an avoidance (latency of less than 5 sec). Figure 13 shows the average proportion of trials out of the total of 60 trials that fell into each of the categories for each group. An analysis of variance (2 X 2 X 2; main effects of sex, radiation, and restraint) was performed on each of these measures. The number of responses to a criterion of 8 avoidances in 10 trials was also analyzed by sex and treatment.

The number of avoidances differed significantly for sex ($p<.05$) and treatments ($p<.01$) as shown in Figure 14. With the exception of the restraint condition, the males showed fewer avoidances than the females. All treatment groups avoided less frequently than sham controls. The reduction was greatest in the irradiated and the combined restraint plus irradiated groups. Although radiation and restraint each had deleterious effects on avoidance performance, the performance decrement was not increased by combining the treatments.

Failures to respond were less frequent among females ($p<.001$) and more frequent in the irradiated groups ($p<.001$) (Fig. 15). There was also a sex X irradiation interaction ($p<.05$). Figure 15 shows that in contrast to the other groups, the restrained females responded much the same with or without irradiation.

After a succession of avoidances without receiving a shock (US), many theorists assume that an animal has demonstrated learning. We chose the fairly common learning criterion of 8 avoidances in 10 trials. By this criterion, 44% of the sham controls, 17% of the restraint stressed, 5% of the irradiated, and 22% of the restraint stressed plus irradiated subjects were classified as having learned the task. The number of trials to reach criterion was significantly greater for irradiated subjects ($p<.01$). Although the mean number of trials to reach criterion was the lowest among sham control females, the large variability in individual scores obscured any differences.

In summary, the results on avoidance conditioning were consistent in showing both a sex difference and an effect of irradiation. Restraint, while not itself significantly affecting avoidance conditioning, was a contributing factor to sex and radiation interactions. The different response in males and females to the combination of radiation and restraint stressors is best seen in Figures 10 and 15, where responses of each sex with and without restraint are plotted as a function of irradiation condition. The females'

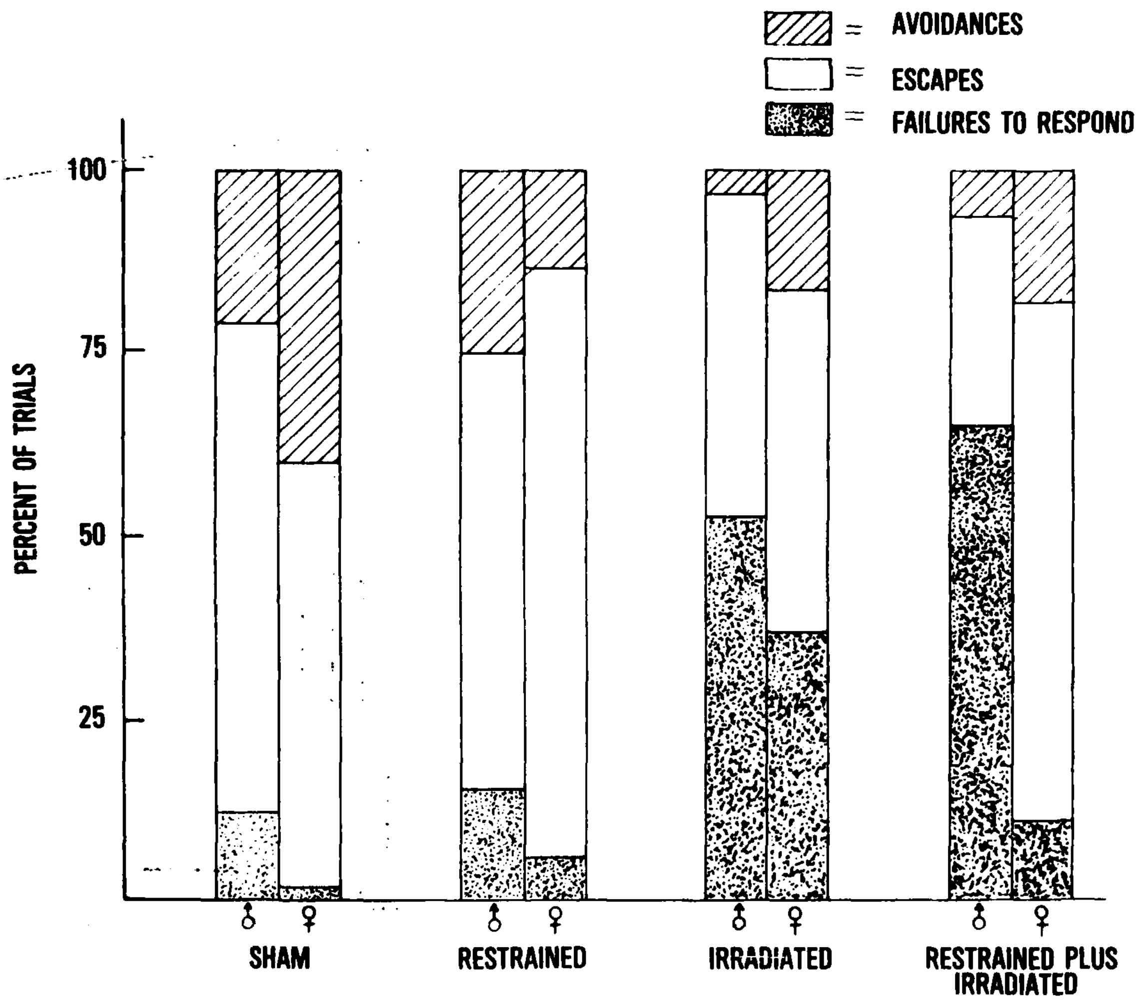

Figure 13. The percentage of avoidances, escapes, and failures to respond during 60 trials of avoidance conditioning by male and female rats in sham control, restraint stressed, irradiated, and both restrained and irradiated conditions.

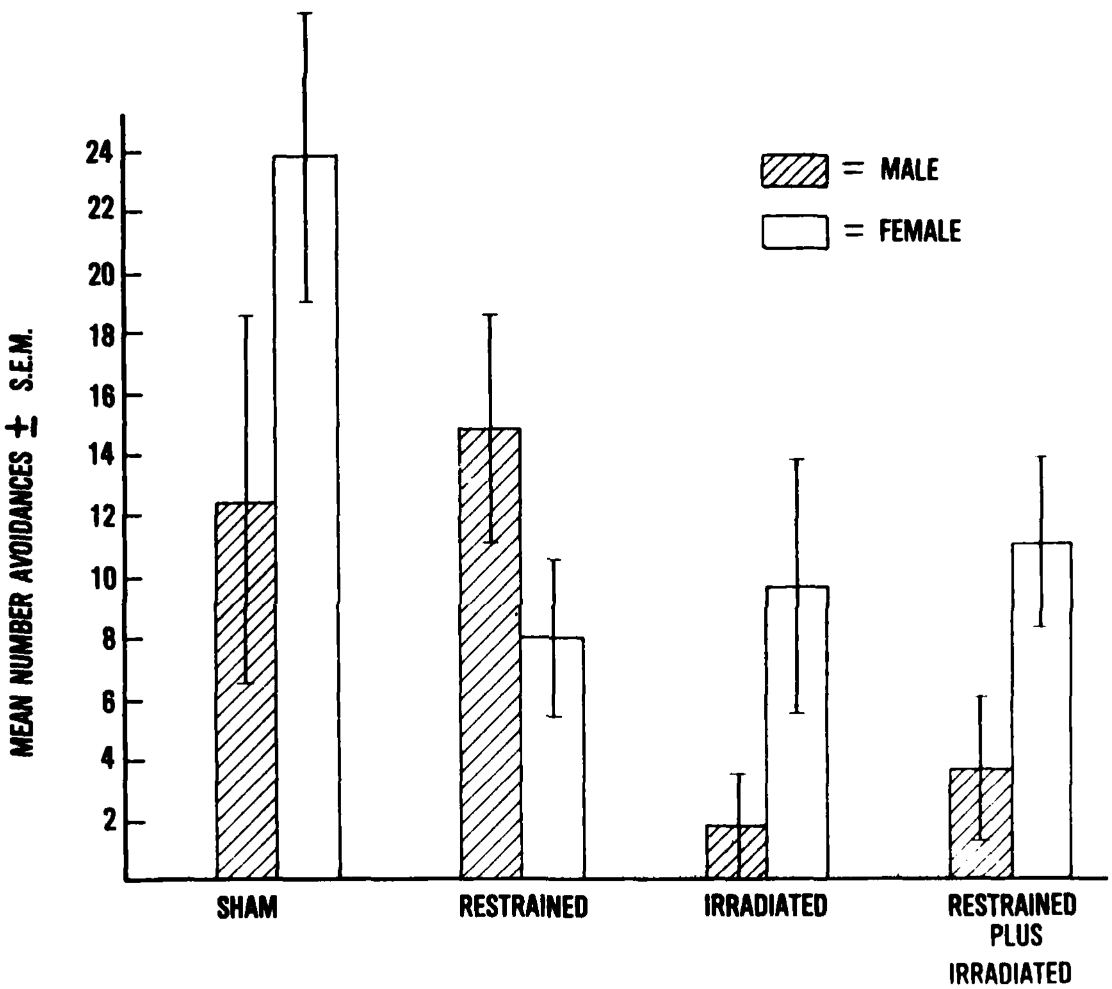

Figure 14. A comparison of the mean number of avoidances (± 1 S.E.M.) during 60 trials for male and female rats in each of the experimental conditions.

latencies were longest following irradiation, but latencies following combined stressors were equivalent to the shorter latencies shown after restraint (Figs. 9, 10, 11, view D, and 15). Males also showed long response latencies following irradiation but combined stressors resulted in even longer latencies (Figs. 10, 11, views C and D, and 15). Failures to respond predominated and there were no response changes over time indicative of learning in the male irradiated and combination groups. Irradiated females were more likely to make a response than their male counterparts (Figs. 13 and 15). It appeared that learning deficits occurred in both sexes but were more likely to be expressed in male subjects as a failure to respond and in female subjects as a longer response latency.

Adrenal Weights and Gastric Lesions

Following behavioral testing, the animals were killed, their adrenal glands removed for weighing, and their stomachs examined for lesions. An analysis of variance for main effects of sex and treatment was performed for each measurement. There were no significant effects on adrenal weights, but there was a significant treatment effect on numbers of ulcers ($p<.05$).

A stomach lesion typically consisted of an erosion of the first mucosal layer of the ruminary area of the stomach. Histological examination of several lesions showed breakage of small capillaries and accompanying hematoma. These ulcers did not penetrate the stomach walls. There were no significant sex differences in the occurrence of ulcers so the data for both sexes were combined (Fig. 16). Ulcer incidence was much higher in the restraint stressed groups. The low incidence in irradiated and restrained plus irradiated was below that expected by comparison to the approximately 10% incidence in the sham control group. It was particularly difficult to understand why those restrained plus irradiated did not have at least the same number of ulcers as those merely restrained since they were restrained prior to irradiation and there should not have been time for healing to occur before necropsy. The association between ulcer incidence and performance decrements seen in our previous study (25) was not present.

Adrenocortical activation typically is seen following any type of stressor, including ionizing radiation. Measuring adrenal weights two hours poststress probably was too soon for neuroendocrine changes to be reflected at the gross morphological level. Following exposure to approximately the same amount of ionizing radiation as in the current experiment, Malatova et al. (32) found increases in plasma and adrenal corticosterone to a maximum level 60 min after irradiation. However, significant increases in adrenal weights were not found until 24 hr after irradiation (32).

DISCUSSION

Theoretical Considerations

There are precedents for viewing ionizing radiation in a stress paradigm and for examining its effects in combination with other stressors. The reticuloendothelial system (RES) and the neuroendocrine system have provided theoretical physiological integrating mechanisms cited by previous

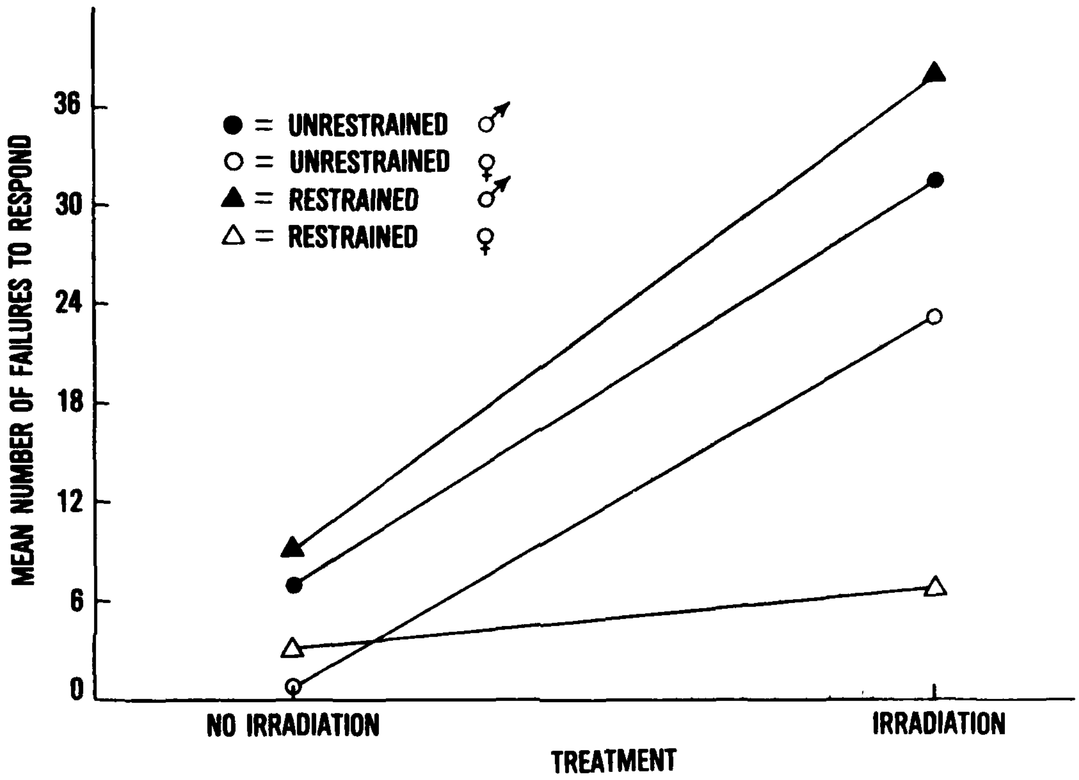

Figure 15. A comparison of the mean number of failures to respond during 60 avoidance conditioning trials for male and female rats as a function of restraint and irradiation condition.

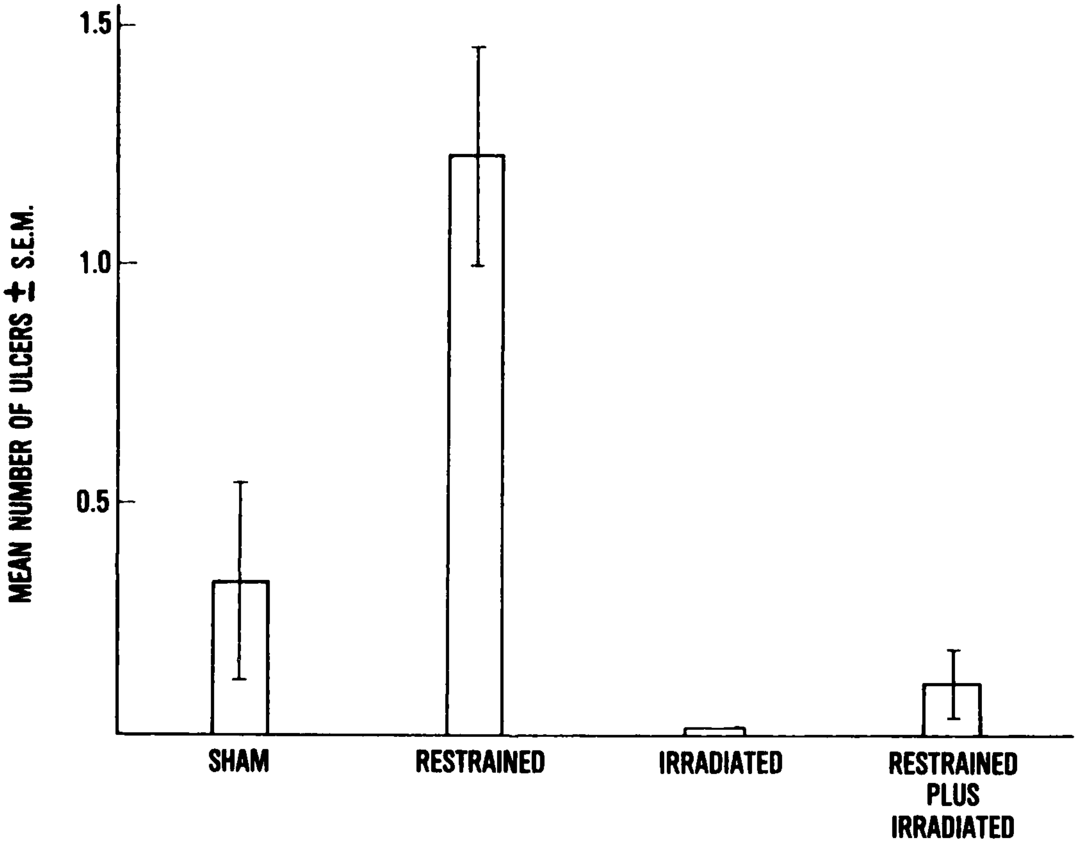

Figure 16. The mean number (± 1 S.E.M.) of stomach ulcers found in subjects of sham control, restraint stressed, irradiated, and both restrained and irradiated conditions.

researchers. Although our experiment was not designed to assess changes in either of these systems, we will briefly review other experiments and compare our results to them. Our major results, a decrement in avoidance conditioning following irradiation and a sex difference in avoidance conditioning most evident in the combination of restraint with irradiation, will be systematically explored.

The RES is a general theoretical concept that encompasses the blood immune system. It rarely is referred to in state-of-the-art immune research where specific variables are isolated and quantified (e.g., an increase or decrease in T-lymphocytes). It is frequently cited in the older literature and still serves to emphasize a complex series of interactions that are functionally related. The radiation exposure used in this study was within the range where the predominant physiological effects were hematopoietic (1). Radiation severely depresses the blood immune system, and Patterson (38) proposed that exhaustion of RES cells is the prime cause of death after whole body irradiation.

Drum-trauma refers to a stressing technique in which rats are tumbled in cylindrical drums. Reichard (41) showed that rats made resistant to drum-trauma showed decreased radiation lethality mediated by parts of the RES. After about 750 revolutions at 40 rpm, animals displayed a typical picture of shock and died shortly after they were removed from the drum. If rats were subjected to repeated sublethal doses of tumbling, resistance to this stress was acquired and they could be tumbled over 1,000 revolutions without fatality (36, 42). Boiled acidified extracts of spleen and plasma from trauma-resistant rats increased the survival of normal rats when injected in these animals prior to drum-trauma (42) or prior to irradiation (41).

Whaley et al. (51), in a behavioral experiment, found that rats adapted to the stress of being tumbled in a drum showed decreased saccharin avoidance following irradiation when compared to controls. They postulated that there exists a basic component common to many forms of trauma, such that a cross resistance or nonspecific immunity to stress is possible.

The RES interacts with the neuroendocrine system in determining both physiological and behavioral responses to stress. The neuroendocrine system may be the common pathway through which diverse stressors act to influence dependent variables as disparate as immune responses and avoidance conditioning behaviors. In his classic studies, Selye (47, pp. 101-102) found that removal of the adrenal glands prevented typical stress changes in the thymus, and removal of the pituitary prevented stimulation of the adrenal glands by stress.

The unconditioned stimulus (shock) in the shuttle-box is an environmental stressor to which a rat typically learns the appropriate avoidance response. The ability to learn this response is changed by subjecting the animals to prior stressors (25) or by direct pharmacological manipulation of the pituitary-adrenal system (2, 3, 10, 11, 21). ACTH facilitates acquisition of an active avoidance response and delays extinction of that response. Corticosteroids, in addition to inhibiting avoidance acquisition (10), depress the RES (34). Other steroids, notably estrogen, are RES stimulants (34).

Park and Scarborough (37) showed that RES stimulation and depression had opposite effects on a conditioned emotional response. The ability to adapt behaviorally to stress appears to parallel physiological adaptation.

Although it has not been previously shown at this level of irradiation, it was not surprising that our irradiated animals showed decrements in avoidance conditioning. In addition to effects on the RES, other researchers have shown that, behaviorally, ionizing radiation is a noxious, stress-producing stimulus (18, 19). Avoidance conditioning has been determined both in our laboratory and the laboratories of others to be a stress-sensitive task (10, 25).

Another finding of interest was that the performance following the combination of stressors (restraint plus irradiation) was not what might have been expected from adding the effects obtained from two stressors individually. Becq and Betz (4) observed a decrease in adrenocortical response to irradiation stress if another stressor had been applied before irradiation. Reichard (41) reduced radiation lethality by using steroids or by activating the immune system with a mild stressor. Mickley (33) has speculated that the improvement of postirradiation performance following antihistamine administration (12, 27) could be due to its influence on the endocrine system.

It has been noted for some time that females of reproductive age have an enhanced immune responsiveness. Nicol et al. (35) suggested that the estrogen molecule has two biochemical components: one which is active in the immune system and the other in the reproductive system. The adrenal cortex secretes androgens and estrogens in both sexes, but the additional gonadal secretion of estrogen in females may underlie their greater immune responsiveness. Higher levels of circulating estrogens have been shown to prolong the life of animals exposed to potentially lethal doses of radiation (43) and to be important in maintaining vascular tone and blood pressure during circulatory stress (50).

If the RES affects performance following radiation and stress, the higher level of circulating estrogens would lead us to expect behavioral differences between sexes in the direction of better performance for females. Mickley (33) found decrements in performance that were more severe for male than female rats following 10,000 rads of ionizing radiation. In gonadectomized males, estradiol injections raised performance level to that of the females. Ovariectomy was found to reduce female performance to that of males (33). Park and Scarborough (37) returned performance on a conditioned emotional response to normal by giving adrenalectomized, gonadectomized male subjects a RES stimulant. In this experiment, irradiated females showed less grooming in the activity maze and better avoidance acquisition when in the shuttlebox. The most profound difference was seen when restraint stress and radiation were combined (see Figs. 9 and 11, view D). Performance of males was at its poorest, lower than that of the males in the irradiated group and lower than the performance of females receiving the combination treatment. Conversely, females showed the largest decrements following irradiation alone. It appeared that restraint stress adds to radiation stress for males but decreases radiation stress for females.

To discuss the opposite effect of restraint on irradiated males and females, we also need to consider the unexpected lack of significant effect from the restraint condition alone. The subjects in the condition with 8 hr of restraint had the highest number of stomach ulcers but, unlike similarly treated subjects in our previous study (25), did not show a behavioral decrement. Procedural differences between the two studies may be important. To control for the extraneous variables involved in the radiation exposure procedure, each of the subjects in this study was placed in plastic carriers for about 50-min on three separate occasions prior to treatment. Although the restraint technique was different from the carrying technique, both were physically confining and there may have been some generalized preadaptation that reduced the stress in the restraint condition to a level below the behavioral threshold. This "preadaptation" may have been a learning phenomenon analogous to that emphasized by Seligman and others in building a resistance to learned helplessness (31, 45). Using this interpretation, the three experiences of release from restraint and subsequent experiences of safety would have changed the animal's expectations and reduced the perceived threat of restaint. Selye's work (46, 47) allows a more directly physiological interpretation: the mobilization of the body's resources following stress provides a period of increased resistance to stress. In this view, the experience of being restrained in the carriers "primed" the system--increasing pituitary/adrenal and RES activation--so that the 8 hr of restraint was not as detrimental as in the previous experiment (25).

Bear in mind that a mild stressor can either depress or enhance responses to further stressors. Then, a reexamination of Figures 9 and 11 gives us some evidence that there was some behavioral effect of restraint: (a) following restraint, mean response latencies in females increased, so that their performance matched the previously slower males in the sham control group; (b) the response latency of the males in the combined restraint plus irradiation condition was greater than the latency following irradiation alone; (c) the superior performance of females in the restraint stressed plus irradiation group relative to that of the group receiving irradiation alone may be viewed as an immunizing effect of a preirradiation stressor. The addition of a stress to a system that is highly immune responsive should have a stimulating effect, while the same stress to a less responsive system should merely increase the load and further depress the capabilities.

Military Implications

The total combat environment is a complex situation involving the interaction of many stressors, and performance cannot be predicted by considering them in isolation. Combat is a stressful psychological situation that demands physical and mental performance in hazardous environments that include the agents of modern warfare such as ionizing radiation and chemical weapons. This study has shown both that one stressor may increase the deleterious effects of another stressor and that one stressor may "immunize" and decrease the deleterious effects of the second stressor. Further research is necessary to determine ways to optimize stress interactions. The results we obtained on performance are suggestive of underlying physiological and biochemical interactions. We suggest that (a) future investigators

should measure sensitive histological and biochemical indices in concert with behavior; and (b) particular attention needs to be given to quantifying the stressors and the time course of their effects. Selye (46, 47) has shown that in the general adaptation syndrome, the same stressor can either enhance resistance or precipitate exhaustion depending on the organism's state of immune responsiveness. Psychoneuroendocrinologists (see 49 for review) have found that the underlying homeostatic rhythms are a major source of variability. Thus time of day, as well as length and degree of stress, has a potent influence on performance.

CONCLUSION

In an experiment with albino rats, we have tried to model a nuclear attack scenario in which military personnel receiving 600 to 800 rads of ionizing radiation would be making a counterattack under the stress of an emergency situation. We used a dose of radiation which, though higher than the human exposure field, was estimated to be physiologically equivalent. Restraining the rat in an immobile position, a technique previously shown to have stressing qualities for rats, was chosen as an analogy to the stress of being in a war emergency. Activity and conditioned avoidance acquisition were chosen as test responses.

Performance in the activity maze was only affected to a minor degree and in the direction of considering irradiation as activating. However, all irradiated groups showed retarded conditioned avoidance acquisition which can be interpreted as decreased adaptability to a stressful situation. Furthermore, our results supported the expectation of performance decrements in the military scenario that could not be predicted by considering ionizing radiation in isolation. On the avoidance task, male rats in the combination stress-irradiation condition showed more failures to respond and longer response latencies than any other group. Conversely, female rats showed shorter escape/avoidance latencies in the combined stress-irradiation condition than in the irradiation condition alone. The sex difference may be useful as a clue for investigating mechanisms of radiation resistance and interactions between stressors.

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